

Commentary

Title:

The tough body at the epicentre of amyotrophic lateral sclerosis

Sub-title:

The corpus callosum is a signpost to the interhemispheric highways underpinning the widespread cerebral pathology that typifies the syndrome of ALS.

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The brain has become axiomatic to understanding pathogenesis in amyotrophic lateral sclerosis (ALS), not least given the clinical, molecular and genetic overlap with frontotemporal dementia (1). ALS, although defined in part by its lower motor neuron degeneration, now appears misfiled alongside the neuromuscular disorders. The corpus callosum (CC, Latin translation: tough body) is a pervasive cerebral integrator, and a consistent part of the *in vivo* cerebral white matter MRI signature of ALS (2), noted in *post mortem* studies many decades prior to diffusion tensor imaging (DTI) (3, 4). The paper by Zhang et al on page XXX uses advanced MRI analysis to explore symmetrical interhemispheric functional connectivity in ALS in relation to the regional anatomy of the CC (insert ref).

Loss of interhemispheric connectivity in ALS was initially demonstrated in patients using transcranial magnetic stimulation (5). The identification of regionally coherent MRI blood oxygenation level-dependent (BOLD) signals in a task-free state (resting-state functional MRI) has been a major driver in understanding brain function as a series of network-based processes. This technique first identified interhemispheric impairment between bilateral sub-regions of the primary motor cortex in ALS (6). MR tractography can be used to parcellate the CC and create a cross-sectional 'key' to all structurally connected regions of the brain (7). Zhang and colleagues combined aspects of both approaches, creating a novel voxel mirrored homotopic map to study the symmetrical functional connectivity of regions in relation to the position of their interhemispheric fibres within five regions along the midline sagittal plane of the CC. The central motor cortical interhemispheric fibres were the most consistently involved in combined functional and structural analysis, the latter in keeping with a

previous study focused on this CC regionality (8), and the area where the inflammatory infiltrates appear concentrated (9).

Subcortical structures including the putamen also showed reduced symmetrical functional connectivity and between the superior temporal gyri, the latter aligning with the recognition of consistent verbal fluency impairments in ALS. Cognition was not explored in this study (those with significant cognitive impairment were excluded), though more anterior regions of the CC have been previously linked to measures of frontal lobe dysfunction in ALS (10). Nonetheless, symmetrical functional connectivity changes were noted by Zhang and colleagues in multiple bihemispheric regions connected through both anterior and posterior parts of the CC, as one would predict with the concept of ALS as a widespread cerebral network disorder, despite its motor-predominant phenotype.

The authors point out that the brain is not symmetrical, which may distort phenotype correlations in relation to VMHC mapping. The onset of symptoms in ALS is typically focal and strikingly asymmetric for the two thirds of patients with limb onset. Limb dominance influences laterality of first weakness in upper limb-onset ALS (11) and there is a higher probability of contralateral versus ipsilateral sequential limb involvement (12, 13). The DTI white matter signature is consistently symmetrical however (14). This may reflect group-level analysis in what is a clinically heterogeneous syndrome. Furthermore, there is an average diagnostic delay of around one year in ALS, so that bihemispheric pathology (if not symptoms as well) may be established by the time individuals reach the MRI scanner. With evolving

ideas about trans-synaptic transmission of pathology in ALS, a natural question is whether the CC facilitates interhemispheric spread. A potentially disease-modifying effect of callosotomy in the pre-symptomatic period is then a compelling concept, and testable in appropriate non-human models.

In the context of assessing the effects of other therapeutic interventions the CC, uniquely spanning the breadth of ALS cerebral pathology, warrants further assessment as both a phenotype stratifying and potentially pharmacodynamic biomarker.

References

1. Burrell JR, Halliday GM, Kril JJ, Ittner LM, Gotz J, Kiernan MC, et al. The frontotemporal dementia-motor neuron disease continuum. *Lancet*. 2016;388(10047):919-31.
2. Filippini N, Douaud G, Mackay CE, Knight S, Talbot K, Turner MR. Corpus callosum involvement is a consistent feature of amyotrophic lateral sclerosis. *Neurology*. 2010;75(18):1645-52.
3. Smith MC. Nerve fibre degeneration in the brain in amyotrophic lateral sclerosis. *JNeurolNeurosurgPsychiatry*. 1960;23:269-82.
4. Turner MR. Nerve fibre degeneration in the brain in amyotrophic lateral sclerosis. *Journal of neurology, neurosurgery, and psychiatry*. 2012;83(4):382.
5. Wittstock M, Wolters A, Benecke R. Transcallosal inhibition in amyotrophic lateral sclerosis. *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology*. 2007;118(2):301-7.
6. Jelsone-Swain LM, Fling BW, Seidler RD, Hovatter R, Gruis K, Welsh RC. Reduced Interhemispheric Functional Connectivity in the Motor Cortex during Rest in Limb-Onset Amyotrophic Lateral Sclerosis. *Front Syst Neurosci*. 2010;4:158.
7. Chao YP, Cho KH, Yeh CH, Chou KH, Chen JH, Lin CP. Probabilistic topography of human corpus callosum using cytoarchitectural parcellation and high angular resolution diffusion imaging tractography. *Human brain mapping*. 2009;30(10):3172-87.
8. Muller HP, Unrath A, Huppertz HJ, Ludolph AC, Kassubek J. Neuroanatomical patterns of cerebral white matter involvement in different motor neuron diseases as studied by diffusion tensor imaging analysis. *Amyotrophic lateral*

sclerosis : official publication of the World Federation of Neurology Research Group on Motor Neuron Diseases. 2012;13(3):254-64.

9. Sugiyama M, Takao M, Hatsuta H, Funabe S, Ito S, Obi T, et al. Increased number of astrocytes and macrophages/microglial cells in the corpus callosum in amyotrophic lateral sclerosis. *Neuropathology*. 2013;33(6):591-9.
10. Kolind S, Sharma R, Knight S, Johansen-Berg H, Talbot K, Turner MR. Myelin imaging in amyotrophic and primary lateral sclerosis. *Amyotrophic lateral sclerosis & frontotemporal degeneration*. 2013;14(7-8):562-73.
11. Turner MR, Wicks P, Brownstein CA, Massagli MP, Toronjo M, Talbot K, et al. Concordance between site of onset and limb dominance in amyotrophic lateral sclerosis. *Journal of neurology, neurosurgery, and psychiatry*. 2010;82(8):853-4.
12. Turner MR, Brockington A, Scaber J, Hollinger H, Marsden R, Shaw PJ, et al. Pattern of spread and prognosis in lower limb-onset ALS. *Amyotrophic lateral sclerosis : official publication of the World Federation of Neurology Research Group on Motor Neuron Diseases*. 2010;11(4):369-73.
13. Devine MS, Kiernan MC, Heggie S, McCombe PA, Henderson RD. Study of motor asymmetry in ALS indicates an effect of limb dominance on onset and spread of weakness, and an important role for upper motor neurons. *Amyotrophic lateral sclerosis & frontotemporal degeneration*. 2014;15(7-8):481-7.
14. Menke RA, Korner S, Filippini N, Douaud G, Knight S, Talbot K, et al. Widespread grey matter pathology dominates the longitudinal cerebral MRI and clinical landscape of amyotrophic lateral sclerosis. *Brain*. 2014;137(Pt 9):2546-55.